

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203100Orig1s000**

**CHEMISTRY REVIEW(S)**

## MEMORANDUM

**Date:** August 26, 2012

**To:** NDA 203-100

**From:** Terrance Ocheltree, Ph.D., R.Ph.  
Director  
Division of New Drug Quality Assessment II  
ONDQA

**Subject:** Tertiary review and Concurrence of ONDQA recommendation for NDA 203-100, Stribild™ (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) is an immediate release tablet containing elvitegravir 150 mg (EVG), cobicistat 150 mg (COBI), emtricitabine 200 mg (FTC), and tenofovir disoproxil fumarate 300 mg.

I have assessed the ONDQA reviews of NDA 203-100 by Celia N. Cruz, Ph.D. Milton Sloan, Ph.D., Fuqiang Liu, Ph.D., and Deepika Lakhani, Ph.D. The initial ONDQA review was entered into DARRTS on July 02, 2012, with a recommendation for a Complete Response due to an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites. The label is adequate from an ONDQA perspective. The ONDQA Biopharmaceutics review is included in the initial ONDQA review. A second CMC review was entered into DARRTS on August 24, 2012 updating the status of the recommendation from the Office of Compliance. On August 21, 2012 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES.

Stribild, NDA 203-100, is proposed for use as part of a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve and who have no known substitutions associated with resistance to the individual components of this fixed-dose combination.

The proposed drug product contains four drug substances, elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate. During the NDA review, the applicant withdrew (b) (4) as a drug substance manufacturing site after the Office of Compliance identified GMP deficiencies at that site. The relevant information for the drug substance is presented below:

- Elvitegravir (EVG), a new molecular entity, is referenced to DMF 25187. The DMF was reviewed and found adequate on July 2, 2012. Elvitegravir drug substance is manufactured at three manufacturing sites, Gilead (b) (4). A retest period of (b) (4) months at the recommended storage condition, (b) (4) is assigned.
- Cobicistat (COBI), a new molecular entity, is referenced to DMF 25188 and is defined as Cobicistat on Silicon Dioxide. Cobicistat is manufactured at three manufacturing sites, Gilead (b) (4). A retest period of (b) (4) months is assigned for cobicistat on silicon dioxide when stored at the recommended storage condition (b) (4).

- Emtricitabine (FTC) drug substance information is referenced to the approved NDA 21-752, Truvada. A retest date of (b) (4) months (b) (4) is assigned
- Tenofovir Disoproxil Fumarate (TDF) drug substance information is referenced to the approved NDA 21-356. A retest date of (b) (4) months (b) (4) is assigned.

Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) is an immediate release tablet containing elvitegravir 150 mg (EVG), cobicistat 150 mg (COBI), emtricitabine 200 mg (FTC), and tenofovir disoproxil fumarate 300 mg (TDF, equivalent to 245 mg of tenofovir disoproxil). The tablets are green, capsule shaped, film-coated, and debossed with “GSI” on one side and “1”, on the other side. Stribild 150 mg/150 mg/200 mg/300 mg tablets are stored in 30-count, 100 mL white HDPE bottles with desiccant, induction seal and child proof closure. A separate tablet has been developed for Gilead’s export-only (non-USA) Access program. The “Access tablet” is identical in composition and quality to the US tablet except for the color of the film coating and different debossing.

The manufacture of the EVG/COBI/FTC/TDF tablet employs control (b) (4). These are specified with adequately justified ranges and/or targets in the manufacturing process description. (b) (4)

The complete set of stability data provided supports a shelf life of 24 months when stored in the approved container at 25 °C (with excursions permitted 15 to 30 °C). The data is also supportive of a shelf life of 24 months, when stored in the approved container at less than 30 °C. The container label for the US states “Store at 25 °C (77 °F), (see insert)”; the package insert states “Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F)”. The container label for the Access Program states, “Store at less than 30 °C (86 °F)”, which supports use in Climatic Zone III and Zone IV countries.

In addition to the drug product information for US market Stribild™ tablets, NDA 203-100 includes information for an export-only tablet image to be used in the Gilead Access program. The Access tablet information was also reviewed in its entirety and was found to be adequate

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommended drug product shelf life as described above for the proposed commercial product when it is stored at controlled room temperature.

No Phase 4 recommendations are proposed.

The secondary review of the CMC reviews was performed by Stephen Miller, Ph.D. and Rapti Madurawe, Ph.D.

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/s/  
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TERRANCE W OCHELTREE  
08/26/2012

# **NDA 203-100**

## **Stribild™**

**(Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate) Tablet, 150 mg/150 mg/200 mg/300 mg**

**Gilead Sciences, Inc.**

<b>CMC Review Team</b>	<b>Section</b>
<b>Celia N. Cruz, Ph.D.*</b>	<b>Drug Product</b>
<b>Milton Sloan, Ph.D.*</b>	<b>Drug Substance</b>
<b>Fuqiang Liu, Ph.D.*</b>	<b>Drug Substance</b>
<b>Deepika Lakhani, Ph.D.**</b>	<b>Biopharmaceutics</b>

**\*DPA II/Branch V**

**\*\*DPA III/Branch IX**

**Office of New Drug Quality Assessment**

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# Chemistry Review Data Sheet

1. NDA 203-100
2. REVIEW #: 01 Addendum 1
3. REVIEW DATE: August 23, 2012
4. REVIEWERS:

Primary:

<u>Reviewer</u>	<u>NDA CTD Section</u>
Milton Sloan, Ph.D.	Drug Substance: Elvitegravir DMF Drug Substance: Tenofovir DF
Fuqiang Liu, Ph.D.	Drug Substance: Cobicistat DMF Drug Substance: Emtricitabine
Celia N. Cruz, Ph.D.	Drug Product Module 2 Labeling Reference Section Executed Batch Records

Secondary:

<u>Reviewer</u>	<u>Section</u>
Stephen Miller, Ph.D.	Drug Substance: Cobicistat DMF Drug Substance: Emtricitabine
Rapti Madurawe, Ph.D.	Drug Substance: Elvitegravir DMF Drug Substance: Tenofovir DF Labeling Drug Product NDA 203-100 Overall Recommendation

Executive Summary Section

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 103093 COR INDAD-02 (Advice/information Request); Pre-NDA	08-July-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Received Date</u>
SDN 045: Labeling/Package Insert Draft	13-Jul-2012
SDN 046: Quality/Quality Information	18-Jul-2012
SDN 048: Labeling/Package Insert Draft	26-Jul-2012
SDN 049: Quality/Quality Information	02-Aug-2012
SDN 051: Labeling/Package Insert Draft	15-Aug-2012
SDN 053: Labeling/Package Insert Draft	17-Aug-2012
SDN 055: Labeling/Package Insert Draft	22-Aug-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404 USA
Representative:	Christophe Beraud, PhD, Associate Director, Regulatory Affairs Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Telephone:	650 574 3000

8. DRUG PRODUCT NAME/CODE/TYPE:

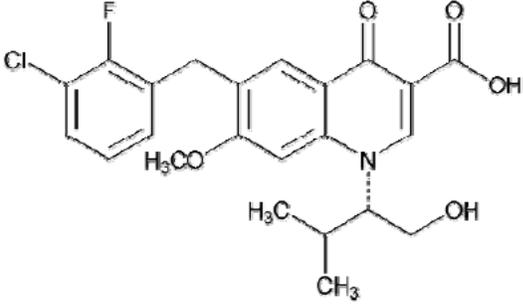
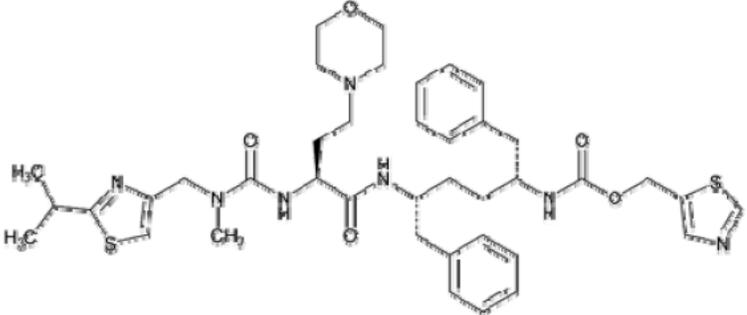
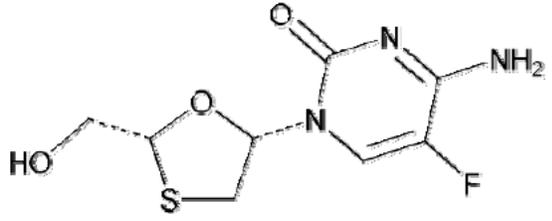
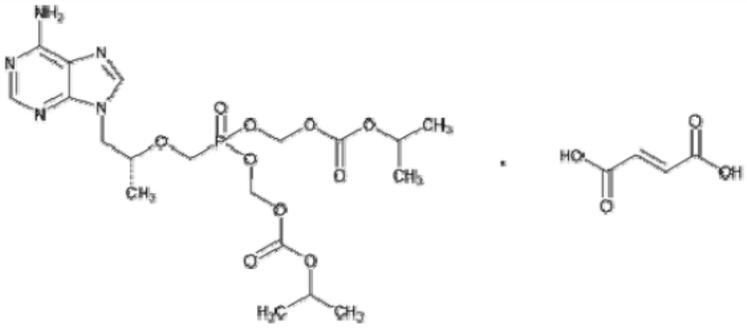
- a) Proprietary Name: Stribild™
- b) Non-Proprietary Name (USAN): Elvitegravir, Cobicistat, Emtricitabine, Tenofovir DF Tablet
- c) Code Name/# (ONDC only): EVG/COBI/FTC/TDF
- d) Chem. Type/Submission Priority:
  - Chem. Type: 1 new molecular entity, 4 new combination

## Executive Summary Section

- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)
10. PHARMACOL. CATEGORY: integrase inhibitor + pharmacokinetic enhancer (booster) + 1 nucleoside analog reverse-transcriptase inhibitor antiretroviral + 1 nucleotide analog reverse-transcriptase inhibitor antiretroviral
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY: 150 mg / 150 mg / 200 mg / 300 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
- SPOTS product – Form Completed
- Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

## Executive Summary Section

<p><b>Elvitegravir:</b>            (1) 3-Quinolincaroxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1<i>S</i>)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-;            (2) 6-(3-Chloro-2-fluorobenzyl)-1-[(2<i>S</i>)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.</p>	 <p style="text-align: center;"><math>C_{23}H_{23}ClFNO_5</math>, MW 447.88</p>
<p><b>Cobicistat:</b>            (1) 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (3<i>R</i>,6<i>R</i>,9<i>S</i>)-;            (2) Thiazol-5-ylmethyl [(1<i>R</i>,4<i>R</i>)-1-benzyl-4-((2<i>S</i>)-2-[(methyl{[2-(1-methylethyl)thiazol-4-yl]methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl] amino]-5-phenylpentyl]carbamate</p>	 <p style="text-align: center;"><math>C_{40}H_{53}N_7O_5S_2</math>, MW 776.02</p>
<p><b>Emtricitabine:</b>            (1) (2<i>R</i>-<i>cis</i>)-4-Amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1<i>H</i>)-pyrimidinone;            (2) 5-Fluoro-1-[(2<i>R</i>,5<i>S</i>)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.</p>	 <p style="text-align: center;"><math>C_8H_{10}FN_3O_3S</math>, MW 247.25</p>
<p><b>Tenofovir Disoproxil Fumarate:</b>            (1) (<i>R</i>)-5-[[2-(6-Amino-9<i>H</i>-purin-9-yl)-1-methylethoxy]methyl]-2,4,6,8-tetraoxa-5-phosphanonanedioic acid, bis(1-methylethyl) ester, 5-oxide, (<i>E</i>)-2-butenedioate (1:1);            (2) Bis(hydroxymethyl) [[(<i>R</i>)-2-(6-amino-9<i>H</i>-purin-9-yl)-1-methylethoxy]methyl]phosphonate, bis(isopropyl carbonate) (ester), fumarate (1:1)            (3) 9-[(<i>R</i>)2[[Bis[[isopropoxycarbonyl]oxy]methoxy]phosphinyl]methoxy]propyl]adenine Fumarate (1:1).</p>	 <p style="text-align: center;"><math>C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4</math>, MW 635.51</p>

## 17. RELATED/SUPPORTING DOCUMENTS:

Executive Summary Section

Refer to Product Quality Review # 1 (02-Jul-2012) for further details on this section; only updates are shown below.

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	Updated LOA 13-June-2012 There is enough data in the application

**B. Other NDA Product Quality Reviews:**

This review is an addendum to Review #1 (02-Jul-2012).

**C. Consults or Outside CMC review team input**

Consult	Recommendation	DATE	REVIEWER
EES	Overall Acceptable	21-Aug-2012	Tara Goen

**D. Other Applications or Submissions Referenced:**

No update to this section since Review #1.

# The Chemistry Review for NDA 203-100

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 203-100 has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Drug Master Files for the elvitegravir and cobicistat drug substances supporting this NDA are adequate. The emtricitabine and tenofovir disoproxil fumarate drug substances are referenced to approved NDAs, and the pending supplements in these NDA's do not impact the approvability of NDA 203-100. The review of the container labels and package insert materials is complete; the Applicant has agreed to all the CMC changes and provided an updated draft label. The overall recommendation from the Office of Compliance is "Overall Acceptable" as of August 21, 2012.

In addition to the drug product information for US market Stribild™ tablets, NDA 203-100 includes information for an export-only tablet image to be used in the Gilead Access program. The Access tablet information was also reviewed in its entirety and was found to be adequate.

Therefore, from the CMC perspective, NDA 203-100 recommended for approval at this time.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Product

##### Drug Product Description

Stribild™ (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) is an immediate-release tablet containing elvitegravir 150 mg (EVG), cobicistat 150 mg (COBI), emtricitabine 200 mg (FTC), and tenofovir disoproxil fumarate 300 mg (TDF, equivalent to 245 mg of tenofovir disoproxil). The tablets are green, capsule shaped, film-coated, and debossed with "GSI" on one side and "1", on the other side.

Executive Summary Section

The Stribild™ 150 mg/150 mg/200 mg/300 mg tablet contains common excipients: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, silicon dioxide, lactose monohydrate, magnesium stearate, and hydroxypropyl cellulose. The film coat contains polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, indigo carmine aluminum lake, and yellow iron oxide. The film coat is added for color and elegance, and has no impact on the drug release rate.

Drug product specifications include tests for: appearance, identification, assay, degradation product, uniformity of dosage units, and dissolution. The degradation product specifications include the total, individual specified, and individual unspecified/unidentified for each drug substance. There are six degradation products specified for COBI, three for FTC, and five for TDF. All the specifications are adequately justified for drug product release and shelf life. EVG has no specified individual degradation products, given that no degradation of this drug substance has been observed at any condition.

NDA 203100 also includes information for an export-only tablet image for the Gilead Access program. The Access tablets are white, capsule shaped, film-coated, and debossed with “GSI” on one side and “1A”, on the other side. The US and Access tablets are differentiated by debossing, color, composition of the coating, and the container labeling. The Access tablets are manufactured using the same process, in-process controls, and container closure system. With the exception of the description for the appearance specification, the drug product specifications and methods are identical.

Drug Product Manufacturing and Control Strategy

The tablets are manufactured (b) (4). Layer 1 contains EVG + COBI and Layer 2 contains FTC + TDF. (b) (4)

(b) (4)

The manufacture of the EVG/COBI/FTC/TDF tablet employs control (b) (4)

(b) (4)

Stribild™ 150 mg/150 mg/200 mg/300 mg tablets are stored in HDPE bottles with desiccant, induction seal and child proof closure. The primary container was demonstrated to provide adequate moisture control upon storage.

## Executive Summary Section

The analytical methods were found to be adequately developed and validated. These methods include content uniformity by HPLC or UPLC, identification by UPLC, UV and TLC, assay by UPLC, degradation product by UPLC, and dissolution by HPLC

Drug Product Stability

Drug product stability data in the primary container system included one batch at 25 °C/60% RH and 30 °C/ 75% RH for 24 months and three additional batches at 25 °C/60% RH and 30 °C/ 75% RH for 12 months. In addition, packaged drug product stability data was provided for 6 weeks at high temperature 50 °C/ambient and high humidity 25 °C/ 80% RH to support the understanding of drug product chemical and physical stability and the adequacy of the container closure system. Open dish studies at 25 °C/60% RH and 30 °C/ 75% RH were included to support understanding of potential degradation and moisture uptake of the tablets.

Overall, the drug product shows no signs of EVG degradation and very limited COBI degradation (b) (4). FTC degradation (b) (4) is observed to a lesser extent in these tablets than in other FTC combination products. Finally, TDF degradation was primarily due to (b) (4). A specification of NMT (b) (4) was established to assure adequate control and prevent degradation of FTC and TDF; the observed tablet (b) (4) was typically less than (b) (4). Finally, there are no significant changes in appearance, assay, or dissolution upon storage. All drug substance process related impurities were demonstrated not to change upon storage of the drug product.

The stability data provided supports a shelf life of 24 months when stored in the approved container at 25 °C (with excursions permitted 15 to 30 °C). The additional stability data also supports a shelf life of 24 months when stored in the approved container at less than 30 °C. The container label for the US states “Store at 25 °C (77 °F), (see insert)”; the package insert states “Store at 25 °C (77 °F), excursions permitted to 15–30 °C (59–86 °F) (see USP Controlled Room Temperature). The container label for the Access Program states, “Store at less than 30 °C (86 °F)”, which supports use in Climatic Zone III and Zone IV countries.

Drug SubstanceElvitegravir (EVG)

Elvitegravir, is a new molecular entity and is not described in any pharmacopeia. Drug substance information was referenced to Gilead’s DMF 25187. The DMF was reviewed and found adequate on July 2, 2012. Elvitegravir drug substance is manufactured at three manufacturing sites, Gilead (b) (4)

Elvitegravir drug substance is a white to pale yellow powder. (b) (4)

Elvitegravir is practically insoluble in aqueous solutions. (b) (4)

Elvitegravir contains (b) (4)

## Executive Summary Section

Elvitegravir is manufactured (b) (4). The critical quality attributes for the elvitegravir manufacturing process were identified to establish a risk assessment for the potential levels of impurities that are likely to be present in drug substance batches during the life cycle of the product. Of the 31 compounds identified as potential impurities, 17 have limits specified and any other impurities will be limited as unspecified impurities. The DMF #25187 authorizes three manufacturing sites, Gilead (b) (4).

The specifications for elvitegravir: appearance, identification, water content, assay, impurity content, enantiomeric purity, residual solvents, (b) (4) heavy metals, residue on ignition, particle size distribution, and differential scanning calorimetry (melting point).

(b) (4)  
Elvitegravir stability studies show no degradation. There were no discernible trends up to 48 months for all stability test attributes at the 25 °C/60% RH long-term storage conditions. Accelerated stability studies at 40 °C/75% RH show only (b) (4) for one impurity after 6 months. (b) (4)

(b) (4) Stress data for elvitegravir show no degradation under (b) (4) conditions. The data supports a retest period of (b) (4) months at the recommended storage condition, (b) (4). Stability data at the accelerated condition support temperature excursions of up to (b) (4) during shipping and handling for up to (b) (4) months.

#### Cobicistat (COBI) as Cobicistat on Silicon Dioxide

Cobicistat (COBI) is a new molecular entity filed under Drug Master File (DMF) 25188. Cobicistat is isolated by adsorption onto silicon dioxide to yield a stable solid form. The drug substance, as defined in DMF 25188, is Cobicistat on Silicon Dioxide. The DMF holder is Gilead, which is also the applicant of NDA 203-100. The adsorption onto silicon dioxide facilitates handling and is suitable for further drug product manufacturing.

DMF 25188 was reviewed on May 31, 2012 to support NDA 203-100. The DMF describes the manufacture and processing of Cobicistat on silicon dioxide. The DMF contained relevant information regarding all aspects of the Cobicistat on silicon dioxide drug substance in support of NDA 203-100.

Review of the DMF identified four potentially mutagenic impurities, (b) (4) are confirmed genotoxic compounds. Gilead (b) (4) provided limited information (b) (4)

(b) (4)

## Executive Summary Section

(b) (4)

Refer to the review of DMF 25188 for more details.

The DMF has addressed the CMC issues conveyed by information request (IR) letters to the DMF holder on January 12, 2012 (Reference ID: 3070278, responded on February 1, 2012), April 26, 2012 (Reference ID: 3121987, responded on May 4, 2012) and May 24, 2012 (Reference ID: 3136051, responded on May 29, 2012); along with the joint Pharm Tox/CMC issues conveyed by information request (IR) letters to the NDA applicant on March 28, 2012 (Reference ID: 3107858, responded on April 26 2012) and May 15, 2012 (Reference ID: 3130687, responded on May 21, 2012). The information submitted to this DMF is adequate to support the use of the Cobicistat on silicon dioxide as a drug substance.

The specifications for cobicistat on silicon dioxide include: appearance, identification of silicon dioxide, identification of cobicistat, water content, assay, impurity content, chiral purity, residual solvents, heavy metals, and bulk density.

Based upon the real-time long-term and accelerated data, along with statistical assessment of the long-term data, a retest period of (b) (4) months is assigned for cobicistat on silicon dioxide when stored at the recommended storage condition (b) (4). Based on the stress studies, temperature excursions and shipping & handling of the DS at temperature of up to (b) (4) may be permitted for up to (b) (4) months. Refer to the review of DMF 25188 for more details.

#### Emtricitabine (FTC)

Most of the chemistry, manufacturing, and controls for emtricitabine drug substance are referred to approved NDA 21-752 for Truvada (tenofovir disoproxil fumarate/emtricitabine) Tablets and NDA 21-500 for Emtriva (emtricitabine) Capsules. The proposed drug substance specification is identical to that in the approved NDA 21-752. There are no outstanding CMC supplements for NDA 21-752 or NDA 21-500 that impact the approvability of NDA 203-100.

Emtricitabine drug substance remains within the established specification when stored at 25 °C/60% RH for up to 36 months. A retest date of (b) (4) months (b) (4) is assigned

#### Tenofovir Disoproxil Fumarate (TDF)

Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25°C. As tenofovir disoproxil fumarate was approved long before the current nomenclature policy, the salt form is used in the nomenclature.

For detailed information regarding the chemistry, manufacturing and controls used in production of Tenofovir Disoproxil Fumarate refer to NDA 21-356. There are no outstanding CMC supplements for NDA 21-356 that impact the approvability of NDA 203-100.

## Executive Summary Section

Stability studies show Tenofovir DF drug substance remains within the established specification limits when stored at 5 °C for up to 36 months. No significant changes in physicochemical properties were observed after 6 months of storage at 25 °C/60% RH. The long-term stability data support the recommended storage condition (b) (4) and the retest period of (b) (4) months.

**B. Description of How the Drug Product is Intended to be Used**

A single Stribild™ (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) 150 mg/150 mg/200 mg/300 mg tablet is taken orally, once daily, with food.

The tablets are packaged in 100 ml, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and 3 grams silica gel desiccant. Each bottle is capped with a white, continuous thread, child-resistant (b) (4) screw cap fitted with an induction seal, (b) (4) liner. The bottle label states that the tablets are to be dispensed in the original container.

The shelf life granted for Stribild 150 mg/150 mg/200 mg/300 mg tablets in the approved container is 24 months when stored at 25 °C (excursions permitted 15 – 30 °C) or at less than 30°C.

**C. Basis for Approvability or Not-Approval Recommendation**

Information provided on drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability to support expiry is adequate. The DMFs for cobicistat and elvitegravir are adequate. Tenofovir disoproxil fumarate and emtricitabine drug substance information was reviewed previously and approved under NDA 21-356 and NDA 21-752, respectively. The labeling was reviewed and CMC comment to the container/carton labels and the packaging inserts were incorporated by the Applicant. Therefore, the Applicant has provided sufficient information for assuring consistent product quality of the four drug substances and the drug product.

As of August 21, 2012, the overall recommendation for manufacturing and testing facilities is “Overall Acceptable”. Therefore, NDA 203100 is recommended for approval from a CMC perspective.

**III. Administrative****A. Reviewer’s Signature**

Celia N. Cruz, Milton Sloan, Fuqiang Liu  
*On file*

**B. Endorsement Block**

Rapti Madurawe

## Executive Summary Section

*On file***C. CC Block***On file*

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/s/  
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CELIA CRUZ  
08/23/2012

MILTON J SLOAN  
08/24/2012

FUQIANG P LIU  
08/24/2012

RAPTI D MADURawe  
08/24/2012

# **NDA 203-100**

**Stribild™**

**(Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate) Tablet, 150 mg/150 mg/200 mg/300 mg,**

**Gilead Sciences, Inc.**

**CMC Review Team**

**Celia N. Cruz, Ph.D.\***

**Milton Sloan, Ph.D.\***

**Fuqiang Liu, Ph.D.\***

**Deepika Lakhani, Ph.D.\*\***

**Section**

**Drug Product**

**Drug Substance**

**Drug Substance**

**Biopharmaceutics**

**\*DPA II/Branch V**

**\*\*DPA III/Branch IX**

**Office of New Drug Quality Assessment**

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# Chemistry Review Data Sheet

1. NDA 203-100
2. REVIEW #: 01
3. REVIEW DATE: July 02, 2012
4. REVIEWERS:

Primary:

<u>Reviewer</u>	<u>NDA CTD Section</u>
Milton Sloan, Ph.D.	Drug Substance: Elvitegravir DMF Drug Substance: Tenofovir DF
Fuqiang Liu, Ph.D.	Drug Substance: Cobicistat DMF Drug Substance: Emtricitabine
Celia N. Cruz, Ph.D.	Drug Product Module 2 Labeling Reference Section Executed Batch Records

Secondary:

<u>Reviewer</u>	<u>Section</u>
Stephen Miller, Ph.D.	Drug Substance: Cobicistat DMF Drug Substance: Emtricitabine
Rapti Madurawe, Ph.D.	Drug Substance: Elvitegravir DMF Drug Substance: Tenofovir DF Labeling Drug Product NDA 203-100 Overall Recommendation

Executive Summary Section

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 103093 COR INDAD-02 (Advice/information Request); Pre-NDA	08-July-2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Received Date</u>
Original: New NDA	26-Oct-2011
SDN 003: Quality/Response to Information Request	17-Nov-2011
SDN 004: Quality/Response to Information Request	22-Nov-2011
SDN 011: Quality/Response to Information Request	23-Jan-2012
SDN 014: Quality/Response to Information Request	30-Jan-2012
SDN 021: Labeling/Package Insert Draft	22-Mar-2012
SDN 023: Labeling/Package Insert Draft	30-Mar-2012
SDN 031: Quality/Response to Information Request	20-Apr-2012
SDN 032: Quality/Response to Information Request	27-Apr-2012
SDN 035: Quality/Response to Information Request	21-May-2012
SDN 037: Quality/Response to Information Request	30-May-2012
SDN 040: Quality/Response to Information Request	13-June-2012
SDN 041: Quality/Quality Information	21-June 2012
SDN 042: Quality/Response to Information Request	28-June-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Gilead Sciences, Inc.
Address:	333 Lakeside Drive Foster City, CA 94404 USA
Representative:	Christophe Beraud, PhD, Associate Director, Regulatory Affairs Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Telephone:	650 574 3000

8. DRUG PRODUCT NAME/CODE/TYPE:

## Executive Summary Section

- a) Proprietary Name: Stribild™
- b) Non-Proprietary Name (USAN): Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF Tablet
- c) Code Name/# (ONDC only): EVG/COBI/FTC/TDF
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1 new molecular entity, 4 new combination
  - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1)

10. PHARMACOL. CATEGORY: integrase inhibitor + pharmacokinetic enhancer (booster) + 1 nucleoside analog reverse-transcriptase inhibitor antiretroviral + 1 nucleotide analog reverse-transcriptase inhibitor antiretroviral

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 150 mg / 150 mg / 200 mg / 300 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

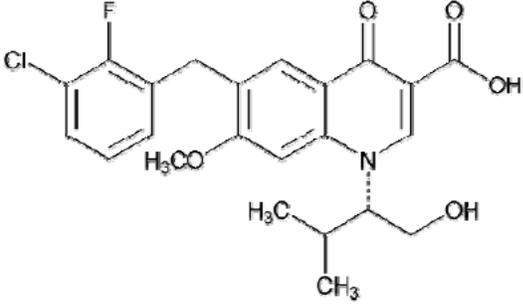
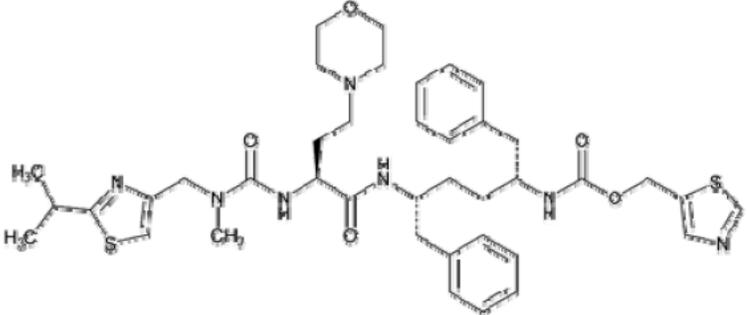
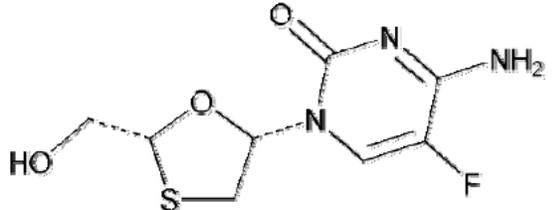
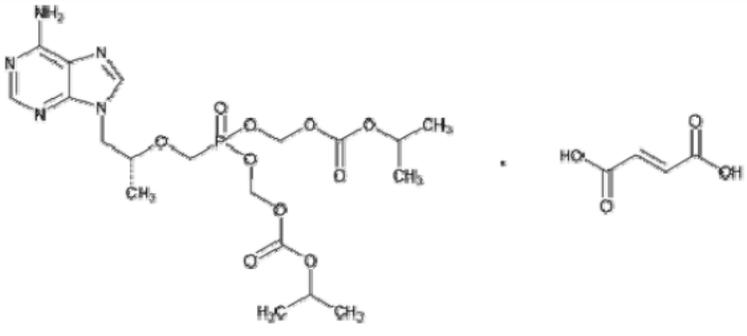
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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<p><b>Elvitegravir:</b>            (1) 3-Quinolincaroxylic acid, 6-[(3-chloro-2-fluorophenyl)methyl]-1,4-dihydro-1-[(1<i>S</i>)-1-(hydroxymethyl)-2-methylpropyl]-7-methoxy-4-oxo-;            (2) 6-(3-Chloro-2-fluorobenzyl)-1-[(2<i>S</i>)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.</p>	 <p style="text-align: center;"><math>C_{23}H_{23}ClFNO_5</math>, MW 447.88</p>
<p><b>Cobicistat:</b>            (1) 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (3<i>R</i>,6<i>R</i>,9<i>S</i>)-;            (2) Thiazol-5-ylmethyl [(1<i>R</i>,4<i>R</i>)-1-benzyl-4-((2<i>S</i>)-2-[(methyl{[2-(1-methylethyl)thiazol-4-yl]methyl} carbamoyl)amino]-4-(morpholin-4-yl)butanoyl] amino]-5-phenylpentyl]carbamate</p>	 <p style="text-align: center;"><math>C_{40}H_{53}N_7O_5S_2</math>, MW 776.02</p>
<p><b>Emtricitabine:</b>            (1) (2<i>R</i>-<i>cis</i>)-4-Amino-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-2(1<i>H</i>)-pyrimidinone;            (2) 5-Fluoro-1-[(2<i>R</i>,5<i>S</i>)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine.</p>	 <p style="text-align: center;"><math>C_8H_{10}FN_3O_3S</math>, MW 247.25</p>
<p><b>Tenofovir Disoproxil Fumarate:</b>            (1) (<i>R</i>)-5-[[2-(6-Amino-9<i>H</i>-purin-9-yl)-1-methylethoxy]methyl]-2,4,6,8-tetraoxa-5-phosphanonanedioic acid, bis(1-methylethyl) ester, 5-oxide, (<i>E</i>)-2-butenedioate (1:1);            (2) Bis(hydroxymethyl) [[(<i>R</i>)-2-(6-amino-9<i>H</i>-purin-9-yl)-1-methylethoxy]methyl]phosphonate, bis(isopropyl carbonate) (ester), fumarate (1:1)            (3) 9-[(<i>R</i>)2[[Bis[[isopropoxycarbonyl]oxy]methoxy]phosphinyl]methoxy]propyl]adenine Fumarate (1:1).</p>	 <p style="text-align: center;"><math>C_{19}H_{30}N_5O_{10}P \cdot C_4H_4O_4</math>, MW 635.51</p>

## 17. RELATED/SUPPORTING DOCUMENTS:

Executive Summary Section

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
25187	II	Gilead	Elvitegravir	1	Adequate	M. Sloan 27-June-2012 M. Sloan 02-Jul-2012	LOA 21-OCT 2011
25188	II	Gilead	Cobicistat on Silicon Dioxide	1	Adequate	F. Liu 31-May-2012	LOA 24-OCT-2011
(b) (4)	IV	(b) (4)	(b) (4)	4	N/A	N/A	LOA 11-JAN-2012: the quantitative composition, ingredient quality standards, and analytical methods submitted in the NDA.
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	LOA 13-May-2011 There is enough data in the application
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	LOA 13-Apr-2012 There is enough data in the application
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	LOA 12-Apr-2012 There is enough data in the application
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	LOA 28-Mar-2012 There is enough data in the application
(b) (4)	III	(b) (4)	(b) (4)	4	N/A	N/A	LOA 05-Apr-2012

Executive Summary Section

(b) (4)				There is enough data in the application
	4	N/A	N/A	LOA 28-Mar-2012 There is enough data in the application

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other NDA Product Quality Reviews:**

Review	Recommendation	DATE	REVIEWER
Biopharmaceutics Final	Updated dissolution specification for Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate	28-June-2012	Deepika Lakhani

**C. Consults or Outside CMC review team input:**

CONSULTS	RECOMMENDATION	DATE	REVIEWER
EES	PENDING sites <div style="background-color: #cccccc; height: 15px; width: 100%;"></div> (b) (4) Gilead Sciences Inc (PN)	14-June-2012 (last EES update)	Zhong Li

Executive Summary Section

	(inspection in-progress)		
Pharm/Tox	Silica Dioxide level: acceptable (b)(4) acceptance criteria: acceptable Genotoxic Impurity: further controls in drug substance refer to DMF reviews and drug substance sections, Process Impurity: recalculate qualified limits with inclusion of body surface area (IR).	March 19, 2012	Mark Powely
Methods Validation	UPLC Method for Identity, Assay, and Degradation Product Acceptable. Report Pending.	Teleconference 30-Apr-2012	James Allgire
Environmental Analysis	Environmental Assessment Review and Finding of No Significance (FONSI)	03-May-2012	Raanan Bloom
Quality Microbiology	N/A		
Biometrics	N/A		
Labeling	N/A		

**D. Other Applications or Submissions Referenced:**

The applications and submissions below were officially referenced in the NDA; they are all held by Gilead Sciences as the Sponsor/Applicant. In addition, a review aid was provided in Module 1 for the cross-referencing of drug substance sections for emtricitabine and tenofovir disoproxil fumarate to their respective NDA's as shown below.

DOCUMENT Referenced	APPLICATION NUMBER	DESCRIPTION
(b) (4)		
Reference not used in CMC review.	IND 67-671	Emtricitabine/Tenofovir Disoproxil Fumarate IND

Executive Summary Section

Reference not used in CMC review.	IND 53-971	Emtricitabine Capsules IND
Reference not used in CMC review.	IND 52-849	Tenofovir Disoproxil Fumarate (PMPA) IND
Ref-002 PreSub, Ref-003 PreSub SDN 000: ORIG [REDACTED] (b) (4)  SUPP - 24 UPLC method [REDACTED] (b) (4)	NDA 21-937	Atripla (EFV/FTC /TDF) Tablets
SDN: 0673; 25 Jan 2012 Environmental Analysis TDF drug substance section (refer to review aid in Mod 1)	NDA 21-356	Viread (TDF) Tablets
FTC drug substance section. (refer to review aid in Mod 1)	NDA 21-500	Emtriva (FTC) Capsule
SUPP - 028 Original discussion and updates for [REDACTED] (b) (4) HPLC/UPLC methods.	NDA 21-752	Truvada (FTC/TDF) Tablets
Reference not used in CMC review.	NDA 21-896	Emtriva (FTC) Oral Solution
Reference not used in CMC review.	NDA 22-577	Tenofovir Disoproxil Fumarate, Powder 40 mg

# The Chemistry Review for NDA 203-100

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

NDA 203-100 has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. The Drug Master Files for the elvitegravir and cobicistat drug substances supporting this NDA are adequate. The emtricitabine and tenofovir disoproxil fumarate drug substances are referenced to approved NDAs, and the pending supplements in these NDA's do not impact the approvability of NDA 203-100. The label is adequate from a CMC perspective, but labeling review has not been completed by the OND review team. The overall recommendation from the Office of Compliance is PENDING as of June 14, 2012, due to outstanding deficiencies with the drug substance manufacturing sites. The establishment deficiencies are still under evaluation by the Office of Compliance. Therefore, from the CMC perspective, this NDA is not recommended for approval at this time.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Product

##### Drug Product Description

Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) is an immediate-release tablet containing elvitegravir 150 mg (EVG), cobicistat 150 mg (COBI), emtricitabine 200 mg (FTC), and tenofovir disoproxil fumarate 300 mg (TDF, equivalent to 245 mg of tenofovir disoproxil). The tablets are green, capsule shaped, film-coated, and debossed with "GSI" on one side and "1", on the other side.

The Stribild 150 mg/150 mg/200 mg/300 mg tablet contains common excipients: microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, silicon dioxide, lactose monohydrate, magnesium stearate, and hydroxypropyl cellulose. The film coat contains polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, indigo carmine aluminum lake, and yellow iron oxide. The film coat is added for color and elegance, and has no impact on the drug release rate.

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Drug product specifications include tests for: appearance, identification, assay, degradation product, uniformity of dosage units, and dissolution. The degradation product specifications include the total, individual specified, and individual unspecified/unidentified for each drug substance. There are six degradation products specified for COBI, three for FTC, and five for TDF. All the specifications are adequately justified for drug product release and shelf life. EVG has no specified individual degradation products, given that no degradation of this drug substance has been observed at any condition.

Drug Product Manufacturing and Control Strategy

The tablets are manufactured (b) (4). Layer 1 contains EVG + COBI and Layer 2 contains FTC + TDF. (b) (4)

The manufacture of the EVG/COBI/FTC/TDF tablet employs control (b) (4)

Stribild 150 mg/150 mg/200 mg/300 mg tablets are stored in HDPE bottles with desiccant, induction seal and child proof closure. The primary container was demonstrated to provide adequate moisture control upon storage.

The analytical methods were found to be adequately developed and validated. These methods include content uniformity by HPLC or UPLC, identification by UPLC, UV and TLC, assay by UPLC, degradation product by UPLC, and dissolution by HPLC

Drug Product Stability

Drug product stability data in the primary container system included one batch at 25 °C/60% RH and 30 °C/ 75% RH for 24 months and three additional batches at 25 °C/60% RH and 30 °C/ 75% RH for 12 months. In addition, packaged drug product stability data was provided for 6 weeks at high temperature 50 °C/ambient and high humidity 25 °C/ 80% RH to support the understanding of drug product chemical and physical stability and the adequacy of the container closure system. Open dish studies at 25 °C/60% RH and 30 °C/ 75% RH were included to support understanding of potential degradation and moisture uptake of the tablets.

Overall, the drug product shows no signs of EVG degradation and very limited COBI degradation (b) (4). FTC degradation (b) (4) is

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observed to a lesser extent in these tablets than in other FTC combination products. Finally, TDF degradation was primarily due to (b) (4). A specification of NMT (b) (4) was established to assure adequate control and prevent degradation of FTC and TDF; the observed tablet (b) (4) was typically less than (b) (4). Finally, there are no significant changes in appearance, assay, or dissolution upon storage. All drug substance process related impurities were demonstrated not to change upon storage of the drug product.

The complete set of stability data provided supports a shelf life of 24 months when stored in approved container at 25 °C (with excursions permitted 15 to 30 °C). The data is also supportive of a shelf life of 24 months, when stored in the approved container at less than 30 °C.

**Drug Substance****Elvitegravir (EVG)**

Elvitegravir, is a new molecular entity and is not described in any pharmacopeia. Drug substance information was referenced to Gilead's DMF 25187. The DMF was reviewed and found adequate on July 2, 2012. Elvitegravir drug substance is manufactured at three manufacturing sites, Gilead (b) (4)

Elvitegravir drug substance is a white to pale yellow powder. (b) (4)

Elvitegravir is practically insoluble in aqueous solutions. (b) (4)

Elvitegravir contains (b) (4)

Elvitegravir is manufactured (b) (4) The critical quality attributes for the elvitegravir manufacturing process were identified to establish a risk assessment for the potential levels of impurities that are likely to be present in drug substance batches during the life cycle of the product. Of the 31 compounds identified as potential impurities, 17 have limits specified and any other impurities will be limited as unspecified impurities. The DMF #25187 authorizes three manufacturing sites, Gilead (b) (4)

The specifications for elvitegravir: appearance, identification, water content, assay, impurity content, enantiomeric purity, residual solvents, (b) (4) heavy metals, residue on ignition, particle size distribution, and differential scanning calorimetry (melting point).

(b) (4)  
Elvitegravir stability studies show no degradation. There were no discernible trends up to 48 months for all stability test attributes at the 25 °C/60% RH long-term storage conditions.

Accelerated stability studies at 40 °C/75% RH show only (b) (4) for one impurity after 6 months. (b) (4)

Stress data for elvitegravir show no degradation under (b) (4) conditions. The data supports a retest period of (b) (4) months at the recommended storage condition, (b) (4) Stability

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data at the accelerated condition support temperature excursions of up to (b) (4) during shipping and handling for up to (b) (4) months.

Cobicistat (COBI) as Cobicistat on Silicon Dioxide

Cobicistat (COBI) is a new molecular entity filed under Drug Master File (DMF) 25188. Cobicistat is isolated by adsorption onto silicon dioxide to yield a stable solid form. The drug substance, as defined in DMF 25188, is Cobicistat on Silicon Dioxide. The DMF holder is Gilead, which is also the applicant of NDA 203-100. The adsorption onto silicon dioxide facilitates handling and is suitable for further drug product manufacturing.

DMF 25188 was reviewed on May 31, 2012 to support NDA 203-100. The DMF describes the manufacture and processing of Cobicistat on silicon dioxide. The DMF contained relevant information regarding all aspects of the Cobicistat on silicon dioxide drug substance in support of NDA 203-100.

Review of the DMF identified four potentially mutagenic impurities, (b) (4) are confirmed genotoxic compounds. Gilead provided limited information (b) (4)

(b) (4)

(b) (4) Refer to the review of DMF 25188 for more details.

The DMF has addressed the CMC issues conveyed by information request (IR) letters to the DMF holder on January 12, 2012 (Reference ID: 3070278, responded on February 1, 2012), April 26, 2012 (Reference ID: 3121987, responded on May 4, 2012) and May 24, 2012 (Reference ID: 3136051, responded on May 29, 2012); along with the joint Pharm Tox/CMC issues conveyed by information request (IR) letters to the NDA applicant on March 28, 2012 (Reference ID: 3107858, responded on April 26 2012) and May 15, 2012 (Reference ID: 3130687, responded on May 21, 2012). The information submitted to this DMF is adequate to support the use of the Cobicistat on silicon dioxide as a drug substance.

The specifications for cobicistat on silicon dioxide include: appearance, identification of silicon dioxide, identification of cobicistat, water content, assay, impurity content, chiral purity, residual solvents, heavy metals, and bulk density.

Based upon the real-time long-term and accelerated data, along with statistical assessment of the long-term data, a retest period of (b) (4) months is assigned for cobicistat on silicon dioxide when stored at the recommended storage condition (b) (4) Based on the stress

## Executive Summary Section

studies, temperature excursions and shipping & handling of the DS at temperature of up to (b) (4) may be permitted for up to (b) (4) months. Refer to the review of DMF 25188 for more details.

### Emtricitabine (FTC)

Most of the chemistry, manufacturing, and controls for emtricitabine drug substance are referred to approved NDA 21-752 for Truvada (tenofovir disoproxil fumarate/emtricitabine) Tablets and NDA 21-500 for Emtriva (emtricitabine) Capsules. The proposed drug substance specification is identical to that in the approved NDA 21-752. There are no outstanding CMC supplements for NDA 21-752 or NDA 21-500 that impact the approvability of NDA 203-100.

Emtricitabine drug substance remains within the established specification when stored at 25 °C/60% RH for up to 36 months. A retest date of (b) (4) months (b) (4) is assigned

### Tenofovir Disoproxil Fumarate (TDF)

Tenofovir disoproxil fumarate (a prodrug of tenofovir) is a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Tenofovir disoproxil fumarate is converted *in vivo* to tenofovir, an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir disoproxil fumarate is a white to off-white crystalline powder with a solubility of 13.4 mg/mL in distilled water at 25° C. As tenofovir disoproxil fumarate was approved long before the current nomenclature policy, the salt form is used in the nomenclature.

For detailed information regarding the chemistry, manufacturing and controls used in production of Tenofovir Disoproxil Fumarate refer to NDA 21-356. There are no outstanding CMC supplements for NDA 21-356 that impact the approvability of NDA 203-100.

Stability studies show Tenofovir DF drug substance remains within the established specification limits when stored at 5 °C for up to 36 months. No significant changes in physicochemical properties were observed after 6 months of storage at 25 °C/60% RH. The long-term stability data support the recommended storage condition (b) (4) and the retest period of (b) (4) months.

## **B. Description of How the Drug Product is Intended to be Used**

A single Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150 mg/150 mg/200 mg/300 mg tablet is taken orally, once daily, with food.

The tablets are packaged in 100 ml, white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and 3 grams silica gel desiccant. Each bottle is capped with a white, continuous thread, child-resistant (b) (4) screw cap fitted with an induction seal, (b) (4) liner. The bottle label states that the tablets are to be dispensed in original container.

**Executive Summary Section**

The shelf life granted for Stribild 150 mg/150 mg/200 mg/300 mg tablets in the approved container is 24 months when stored at 25 °C (excursions permitted 15 – 30 °C). The drug product stability profile also supports a labeled storage condition of less than 30 °C.

**C. Basis for Approvability or Not-Approval Recommendation**

Information provided on drug product manufacturing, raw materials controls and specifications, analytical methods, and drug product stability to support expiry is adequate. The DMFs for cobicistat and elvitegravir are adequate. Tenofovir disoproxil fumarate and emtricitabine drug substance information was reviewed previously and approved under NDA 21-356 and NDA 21-752, respectively. The labeling has not been reviewed by the OND team; but the labeling and container/carton labels are adequate from a CMC-perspective. All labeling comments will be communicated via the label team review. Therefore, the Applicant has provided sufficient information for assuring consistent product quality of the four drug substances and the drug product.

At this time, this NDA is not recommended for approval due to the following: As of June 14, 2012 the overall recommendation for manufacturing and testing facilities is PENDING.

Approval of this NDA is contingent upon an overall evaluation of “acceptable” in EES and the acceptability of the final labeling.

**III. Administrative****A. Reviewer’s Signature**

Celia N. Cruz, Milton Sloan, Fuqiang Liu

*On file*

**B. Endorsement Block**

Rapti Madurawe

*On file*

**C. CC Block**

*On file*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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CELIA CRUZ  
07/02/2012

MILTON J SLOAN  
07/02/2012

FUQIANG P LIU  
07/02/2012

RAPTI D MADURAWA  
07/02/2012

**PRODUCT QUALITY - (Small Molecule)**  
**IQA for NDA 203-100 (Including Filing Checklist)**

<b>NDA Number:</b> 203-100	<b>NDA Type:</b>  Original NDA, 505(b)(1)	<b>Established/Proper Name:</b>  Elvitegravir, Cobicistat, Emtricitabine and Tenofovir Disoproxil Fumarate Tablets
<b>Applicant:</b>  Gilead	<b>Letter Date:</b>  Stamp Date: Oct 27, 2011	<b>GRMP Goal:</b> July 2, 2012  <b>PDUFA Goal:</b> Aug 27, 2012

**CMC Review Team:** Celia Cruz, Milton Sloan and Fuqiang Liu

**Biopharmaceutics Reviewer:** Deepika A. Lakhani

**Compliance Reviewers:** Linda Ng and Zhong Li

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		<ul style="list-style-type: none"> <li>• Yes, justification for proposed starting materials; 30/75%RH long-term stability data</li> <li>• Agreement on established name</li> </ul>

<b>B. FACILITIES*</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Manufacturing sites are described in Section 1.1.2

6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		DS manufacturing sites are described in Section 1.1.2
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		The DP manufacturing site [REDACTED] (b) (4) is included in Section 1.1.2

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	None found. This should not block filing.

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	X		A statement about expected manufacturing quantities for Tenofovir DF is included in Section 1.12.14; this will need to be revised; Categorical Exclusions are provided for the other 3 actives.

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?		X	Refers to the Type 2 DMFs for this information
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refers to the Type 2 DMFs for this information
14.	Does the section contain information regarding the characterization of the DS?	X		Summary; detailed information in DMFs
15.	Does the section contain controls for the DS?	X		Summary; detailed information in DMFs
16.	Has stability data and analysis been provided for the drug substance?		X	Refers to the Type 2 DMFs for this information
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		For both US and Access versions of the tablets
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		The executed production records are provided for the following portions of a single batch (BK1103C): <ul style="list-style-type: none"> <li>➤ manufacturing of emtricitabine/tenofovir disoproxil fumarate (b) (4)</li> <li>➤ elvitegravir (b) (4)</li> <li>➤ (b) (4) film-coating</li> <li>➤ packaging</li> </ul>
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Formulation Development is included in Module 3 Section P2
23.	Have any Comparability Protocols been requested?		X	None found in NDA Regional Information
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		HDPE Bottles of 30 tablets with CR closure; induction seal liner; 3 grams of silica gel desiccant
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		12 month data at 25°C/60%RH and 30°C/75%RH on three primary batches; 24 month data on supportive batch; 4-6 week data on one batch of Access tablets
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		Design space for DP manufacture
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	This should not block filing. We will reference appropriate sections of Module 3 when requesting method verification by the FDA lab.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		The LOA for (b) (4) DMF was requested, and has now been supplied.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
25188	2	Gilead	Cobicistat on Silicon Dioxide		Drug Substance
25187	2	Gilead	Elvitegravir		Drug Substance
Request LOA	4		(b) (4)		Film Coatings

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		Section 1.14
33.	Have the immediate container and carton labels been provided?	X		Bottle Labels for US and Access Program Carton Label for Access Program

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		

35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Fileable
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		There will be several IR comments from the CMC perspective which will be included in either an early IR letter or the filing letter.

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/s/  
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STEPHEN MILLER  
02/15/2012  
IQA

RAPTI D MADURAWA  
02/17/2012

Office of New Drug Quality Assessment  
Product Quality and Manufacturing Memo  
(PQM Memo)

Memo Date: January 30, 2012  
From: Celia N. Cruz, Ph.D.  
Fuqiang Liu, Ph.D.  
Milton Sloan, Ph.D.  
on behalf of the CMC Review Team

Through: Rapti Madurawe, Ph.D., Branch Chief Division V

NDA Number: 203100  
Applicant: Gilead Sciences Inc.

GRMP Date: July 02, 2012  
PDUFA Date: August 27, 2012

**Drug Product Name and Strength:**

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate 150 mg/150 mg/200 mg/300 mg Tablets, also described as EVG/COBI/FTC/TDF tablets.

**Drug Product Introduction:**

The EVG/COBI/FTC/TDF tablet is an immediate release, capsule shaped film-coated bi-layer tablet. Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate equivalent to 245 mg of tenofovir disoproxil. The NDA provides for two tablet images, one for the US market and one for the global market. The differentiation between the images is the film coat composition, de-bossing and the color. The composition of the US to-be-marketed EVG/COBI/FTC/TDF tablets is shown in Table 1 in page 7. The tablet "Layer 1" and "Layer 2" refer to the EVG/COBI and FTC/TDF formulation layers, respectively.

The drug product manufacturing process for the tablets has

(b) (4)

(b) (4)

The Applicant submitted development data in 3.2.P.2.3 regarding design space development

(b) (4)

Development batches, scale up batches, and registration batches were used to confirm ranges of the proposed design space. In the manufacturing process description in 3.2.P.3.3, the Applicant states that "the manufacturing process for EVG/COBI/FTC/TDF

tablets will be conducted near the targets and within the proven acceptable ranges (PARs) studied in the design space evaluation in Section 3.2.P.2.3.” Please refer to Table 2 in page 9 for the claimed operating ranges within the design space and Table 4 in page 13, for the drug product considerations for inspection summary. The considerations for inspection relate to the ability of the Applicant to operate within and maintain a design space, based on their quality management system and in-process controls (Table 3 in page 10). There are no claims of reduced testing schemes, real time release, or use of predictive models based on the design space.

**Drug Substance Introduction:**

With regards to drug substances, the ONDQA CMC Review team is conveying considerations for inspection for the manufacture of drug substances which are new molecular entities only: elvitegravir and cobicistat on colloidal silicon dioxide. The other two drug substances, emtricitabine and tenofovir disoproxil fumarate, are manufactured under well established processes and are approved and managed under other referenced NDA’s.

Elvitegravir:

Elvitegravir is manufactured

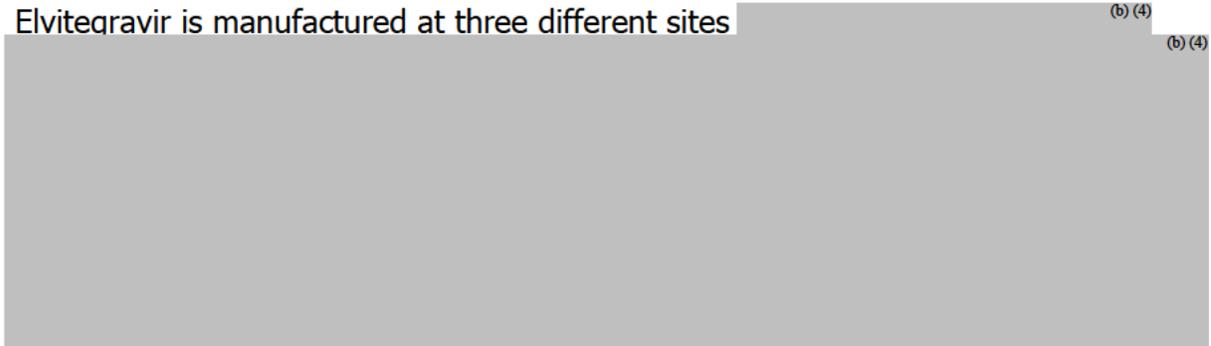
(b) (4)  
(b) (4)



(b) (4) Information regarding the manufacturing process of elvitegravir is referenced to DMF# 025187, which is currently under review to support NDA 203100.

Elvitegravir is manufactured at three different sites

(b) (4)  
(b) (4)



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/s/  
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CELIA CRUZ  
01/30/2012

MILTON J SLOAN  
01/30/2012

FUQIANG P LIU  
01/31/2012

RAPTI D MADURawe  
01/31/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

**METHODS VALIDATION CONSULT REQUEST FORM**

**TO: FDA**  
**Division of Pharmaceutical Analysis**  
**Attn: Benjamin (Nick) Westenberger**  
**Suite 1002**  
**1114 Market Street**  
**St. Louis, MO 63101**

**FROM:** Celia N. Cruz, Methods Validation Requestor, CMC Reviewer  
Steve Miller, Methods Validation Requestor, CMC Lead  
Office of New Drug Quality Assessment (ONDQA)  
E-mail Address: celia.cruz@fda.hhs.gov  
Phone: (301)-796-2143  
Fax.: (301)-796-9745

**Through:** Rapti Madurawe, Branch Chief, Division V  
Phone: (301)-796-1408

**and**

Jeannie David, ONDQA Methods Validation Project Manager  
Phone: 301-796-4247

**SUBJECT:** Methods Validation Request

---

Application Number: NDA 203-100

Name of Product: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate 150 mg/150 mg/200 mg/300 mg Tablets

Applicant: Gilead Sciences, Inc.

Applicant's Contact Person: Christophe Beraud, PhD, Associate Director, Regulatory Affairs

Address: 333 Lakeside Drive, Foster City, CA 94404, USA

Telephone: (650) 522-5093 Fax: (650) 522-5489

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Date NDA Received by CDER: **10/27/2011**

Submission Classification/Chemical Class: NME

Date of Amendment(s) containing the MVP: **10/27/2011**

Special Handling Required: No

DATE of Request: **December 27, 2011**

DEA Class: N/A

Requested Completion Date: **4/27/2011**

**Format of Methods Validation Package (MVP)**

PDUFA User Fee Goal Date: **8/27/2011**

Paper  Electronic  Mixed

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We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

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/s/  
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CELIA CRUZ  
12/27/2011

BALAJEE SHANMUGAM  
12/27/2011

JEANNIE C DAVID  
12/29/2011  
ONDQA Methods Validation Project Manager

**PRODUCT QUALITY - CMC (Small Molecule)  
FILING REVIEW for NDA (ONDQA)**

**NDA Number:**  
203-100

**NDA Type:**  
Original NDA, 505(b)(1)

**Established/Proper Name:**  
Elvitegravir, Cobicistat,  
Emtricitabine and Tenofovir  
Disoproxil Fumarate Tablets

**Applicant:**  
Gilead

**Letter Date:**  
**Stamp Date: Oct 27, 2011**

**GRMP Goal: July 2, 2012**  
**PDUFA Goal: Aug 27, 2012**

**CMC Review Team: Celia Cruz, Milton Sloan and Fuqiang Liu**

**Biopharmaceutics Reviewer: Deepika A. Lakhani**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		<ul style="list-style-type: none"> <li>➤ Justification for proposed starting materials; 30°C/75%RH long-term stability data</li> <li>➤ Agreement on established name</li> </ul>

<b>B. FACILITIES*</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		Manufacturing sites are described in Section 1.1.2

**PRODUCT QUALITY - CMC (Small Molecule)  
FILNG REVIEW for NDA (ONDQA)**

6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			NA
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		DS manufacturing sites are described in Section 1.1.2
8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		The DP manufacturing site <span style="background-color: #cccccc; padding: 0 20px;">(b)(4)</span> is included in Section 1.1.2

**PRODUCT QUALITY - CMC (Small Molecule)  
FILING REVIEW for NDA (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?		X	None found. This should not block filing.

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	Has an environmental assessment report or categorical exclusion been provided?	X		A statement about expected manufacturing quantities for Tenofovir DF is included in Section 1.12.14; this will need to be revised; Categorical Exclusions are provided for the other 3 actives.

**PRODUCT QUALITY - CMC (Small Molecule)  
 FILNG REVIEW for NDA (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?		X	Refers to the Type 2 DMFs for this information
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		X	Refers to the Type 2 DMFs for this information
14.	Does the section contain information regarding the characterization of the DS?	X		Summary; detailed information in DMFs
15.	Does the section contain controls for the DS?	X		Summary; detailed information in DMFs
16.	Has stability data and analysis been provided for the drug substance?		X	Refers to the Type 2 DMFs for this information
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**PRODUCT QUALITY - CMC (Small Molecule)  
FILNG REVIEW for NDA (ONDQA)**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		For both US and Access versions of the tablets
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		The executed production records are provided for the following portions of a single batch (BK1103C): <ul style="list-style-type: none"> <li>➤ manufacturing of emtricitabine/tenofovir disoproxil fumarate (b) (4)</li> <li>➤ elvitegravir (b) (4)</li> <li>➤ (b) (4) film-coating</li> <li>➤ packaging</li> </ul>
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		Formulation Development is included in Module 3 Section P2
23.	Have any Comparability Protocols been requested?		X	None found in NDA Regional Information
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		HDPE Bottles of 30 tablets with CR closure; induction seal liner; 3 grams of silica gel desiccant
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		12 month data at 25°C/60%RH and 30°C/75%RH on three primary batches; 24 month data on supportive batch; 4-6 week data on one batch of Access tablets
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		Design space for DP manufacture

**PRODUCT QUALITY - CMC (Small Molecule)  
FILING REVIEW for NDA (ONDQA)**

28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	
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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		X	This should not block filing. We will reference appropriate sections of Module 3 when requesting method verification by the FDA lab.

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			NA

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		Although not critical, the LOA for (b) (4) DMF should be requested.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
25188	2	Gilead	Cobicistat on Silicon Dioxide		Drug Substance
25187	2	Gilead	Elvitegravir		Drug Substance
Request LOA	4		(b) (4)		Film Coatings

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		Section 1.14
33.	Have the immediate container and carton labels been provided?	X		Bottle Labels for US and Access Program Carton Label for Access Program

**PRODUCT QUALITY - CMC (Small Molecule)  
FILING REVIEW for NDA (ONDQA)**

<b>J. FILING CONCLUSION</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			Fileable
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?	X		There will be several IR comments from the CMC and BP perspectives which will be included in an early IR letter

*{See appended electronic signature page}*

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Stephen Miller, Ph.D.

CMC-Lead

Division of Pre-Marketing Assessment II, Branch V

Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

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Rapti Madurawe, Ph.D.

Branch Chief

Division of Pre-Marketing Assessment II, Branch V

Office of New Drug Quality Assessment

Date

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/s/  
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STEPHEN MILLER

12/16/2011

NDA is fileable from the CMC perspective

RAPTI D MADURawe

12/16/2011